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ORIGINAL ARTICLE

Predicting toxicity of platinum and taxane-based chemotherapy in older patients with gynecologic cancer

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Summary

Purpose: *Since older age is a risk factor for chemotherapy toxicities, a prediction tool that can accurately identify older patients who are at risk for toxicity is necessary. The Cancer and Aging Research Group (CARG) toxicity tool was developed to predict chemotherapy toxicity risk in older patients. However, whether this tool is predictive of the toxicities for patients with specific tumor types who are receiving specific chemotherapy is unclear. This study evaluated whether the CARG toxicity tool is useful for the clinical practice of the gynecologist in predicting toxicity in older patients with gynecologic cancer treated with platinum and taxane-based chemotherapy.*

Methods: *We enrolled 34 patients aged ≥ 65 years with ovarian and endometrial cancer who received platinum and taxane-based chemotherapy into this study. Before starting chemotherapy, each patient was scored using the CARG toxicity tool. The patients were divided into three groups based on the risk of chemotherapy toxicities. We evaluated the associations of each risk group with toxicity incidence, treatment interruption and cycle delay.*

Results: *There was a significant difference in the incidence of two or more grade 3 to 5 toxicities among the risk groups (p=0.0479). Treatment interruption caused by toxicity was also significantly different among the risk groups (p=0.001).*

Conclusions: *Our study confirmed that the CARG toxicity tool could predict chemotherapy toxicity in older patients with ovarian and endometrial cancer treated with platinum and taxane-based chemotherapy. Our results indicate that this tool is useful for the gynecologist in everyday practice.*

Key words: *chemotherapy toxicity, endometrial cancer, older patients, ovarian cancer*

Introduction

With the continued increase in the life expectancy of the world population, the age of patients with cancer is also expected to increase. Regarding the gynecological cancer, the mean age at diagnosis for patients with ovarian and endometrial cancer is older than 60 years [1], and a further increase in the number of ovarian and endometrial cancer patients in the older age group is anticipated. Platinum and taxane-based chemotherapy is one of the standard first-line chemotherapy regimens for ovarian and endometrial cancer [2-5]. Therefore, the number of older patients with ovarian and endometrial cancer treated with platinum and taxane-based chemotherapy may also increase.

Generally, older age is one of the risk factors for chemotherapy toxicity [6-8]. Chemotherapy toxicity may cause treatment delay or interruption, which impairs the efficacy of the treatment, and can endanger the life of older cancer patients. Therefore, identifying the older gynecologic cancer patients who are at risk for platinum and taxane-based chemotherapy toxicity is necessary for the safety of the patients.

Conventional oncology performance status measures, such as the Karnofsky Performance Status (KPS) [9] or the Eastern Cooperative Oncology Group performance status (ECOG-PS) [10], are applied to all cancer patients regardless of patients'

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age to assess functional status, decide eligibility for clinical studies, and make a prediction for the treatment toxicity and patient survival [11-13]. However, whether these measures can be applied for predicting the chemotherapy toxicity, especially in older cancer patients, has not been clarified. Several reports have suggested that these conventional oncology performance status measures could not predict chemotherapy toxicity in older cancer patients [14,15].

To predict morbidity and mortality in older patients, geriatricians perform comprehensive geriatric assessment (CGA), which includes an assessment of the ability for the activities of daily living and instrumental activities of daily living [16]. However, CGA typically has not been used in everyday oncology practice to predict chemotherapy toxicity in older cancer patients, as this assessment is not specialized in predicting the chemotherapy toxicity. Furthermore, completion of all assessments in the CGA takes time.

The Cancer and Aging Research Group (CARG) toxicity tool is a chemotherapy toxicity risk prediction tool that incorporates geriatric and oncologic correlates of vulnerability to chemotherapy toxicity in older cancer patients (Table 1) [17]. The CARG toxicity tool includes the following 11 risk factors: age ≥ 72 years, cancer type (gastrointestinal or genitourinary), standard dosing of chemotherapy, polychemotherapy, hemoglobin levels (males: <11 g/dL; females: <10 g/dL), creatinine clearance of <34 mL/min, hearing impairment self-reported as fair or worse, one or more falls in the last six months, need for assistance in taking medications, limitation in walking one block, and decreased social activities because of physical or emotional health [15,17]. These 11 risk factors are used to classify patients as low, medium, or high-risk for severe chemotherapy toxicity. Hurria et al developed the CARG toxicity tool by evaluating the chemotherapy toxicity of 500 older patients with a solid organ cancer of any type or stage. They showed that the CARG toxicity tool predicted severe chemotherapy toxicity in older cancer patients, and it has also been validated in a similar external cohort [15,17]. However, the populations evaluated in these studies consisted of patients with different tumor types and treatment regimens, so it is still unclear whether the CARG toxicity tool is predictive of the toxicities for patients with specific tumor types who are receiving

Table 1. Scoring system of the CARG toxicity tool [17]

Variable	*Value/Response*	*Score*
Age of patient	≥ 72 years	2
	< 72 years	0
Cancer type	Gastrointestinal or genitourinary cancer	2
	Other cancer types	0
Planned chemotherapy dose	Standard dose	2
	Reduced dose	0
No. of chemotherapy drugs	Polychemotherapy	2
	Monochemotherapy	0
Hemoglobin	< 11g/dl (male), < 10g/dl (female)	3
	≥ 11g/dl (male), ≥ 10g/dl (female)	0
Creatinine clearance (Jelliffe, ideal weight)	< 34 mL/min	3
	≥ 34 mL/min	0
Hearing	Fair, poor, or totally deaf	2
	Excellent or good	0
No. of falls in last 6 months	≥ 1	3
	None	0
Taking medicines	With some help/unable	1
	Without help	0
Walking one block	Somewhat limited/limited a lot	2
	Not limited at all	0
Decreased social activity because of physical/emotional health	Limited at least some of the time	1
	Limited none of the time	0
Total Score		23

CARG: The Cancer and Aging Research Group

specific treatment regimens. Gynecologic cancer patients comprised only 12% of all patients in the development and validation studies of the CARG toxicity tool [15,17]. Furthermore, gynecologic cancer patients had been treated with multiple types of chemotherapy regimens in these studies. Therefore, whether the CARG toxicity tool is predictive of the toxicities of platinum and taxane-based chemotherapy for older gynecologic cancer patients is still unclear.

The aim of this study was to evaluate whether the CARG toxicity tool is useful for the clinical practice of the gynecologist in predicting toxicity in older patients with ovarian and endometrial cancer treated with platinum and taxane-based chemotherapy. We also evaluated whether the CARG toxicity tool is predictive of the treatment delay or interruption induced by chemotherapy toxicity, as these are one of the main causes that impair the efficacy of the treatment.

Methods

Patients

We enrolled 34 patients with ovarian and endometrial cancer into this prospective observational study who had been treated between December 2016 and June 2018. This study was approved by the Ethics Committee of Saitama Medical University International Medical Center, and all patients provided their informed consent prior to the procedures being performed. All procedures were in accordance with the ethical standards of the institutional research committee and with the 1975 Helsinki declaration and its later amendments. All patients were staged by the International Federation of Gynecology and Obstetrics system [18]. Eligible patients were aged ≥ 65 years, had histologically proven ovarian and endometrial cancer, and were scheduled to receive a new or initial chemotherapy regimen. Patients who did not have pathological diagnoses, or who had insufficient clinical data were excluded from this study.

Study design

Prior to starting chemotherapy, each patient was scored using the CARG toxicity tool by study researchers (Table 1). As described above, the CARG toxicity tool was included a validated geriatric assessment questionnaire consisting of six domains: functional status, co-morbidity, psychological state, social activity, social support, and nutrition [15,17]. We stratified the patients into low-risk (score 0-6), medium-risk (score 7-10), and high-risk (score ≥ 11) for chemotherapy toxicity. We also assessed the patients' performance status using ECOG-PS before chemotherapy. Treating oncologists were blinded to the results of the score of CARG toxicity tool and assessed the chemotherapy toxicity graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (ver. 4.0) at each cycle [19].

Statistics

We evaluated the associations of each risk group with the incidence of grade 3 to 5 chemotherapy toxicity, treatment cycle delay and treatment interruption using the chi-square test. STATVIEW (Abacus Concepts, Berkley, CA, USA) was used for data analysis. $P<0.05$ was considered statistically significant.

Results

Patient characteristics

We enrolled 34 gynecologic cancer patients aged ≥ 65 years into this study, including 20 (59%) ovarian cancer and 14 (41%) endometrial cancer patients (Table 2). The mean age of participants was

Table 2. Patient characteristics

Characteristics	*No of patients n (%)*
Age, years	
65-69	16 (47)
70-74	11 (32)
75-79	5 (15)
80-84	2 (6)
Cancer type	
ovarian	20 (59)
endometrial	14 (41)
Cancer stage	
I	12 (35)
II	3 (9)
III	12 (35)
IV	7 (21)
Chemotherapy regimen	
paclitaxel + carboplatin	13 (38)
docetaxel + carboplatin	21 (62)
Lines of chemotherapy	
first line	28 (82)
> first line	6 (18)
Comorbidity	
hypertension	16 (47)
diabetes mellitus	2 (6)
cardiac disease	5 (15)
pulmonary disease	1 (3)
ECOG PS	
0	33 (97)
1	1 (3)
No. of chemotherapy toxicity[a]	
≥1	24 (71)
≥2	15 (44)
≥3	8 (24)

ECOG PS: Eastern Cooperative Oncology Group performance status
[a]Grade 3 to 5 chemotherapy toxicity

71.3 years (range: 65-84). Among the 34 patients, 12 (35%) had stage I, 3 (9%) had stage II, 12 (35%) had stage III, and 7 (21%) had stage IV gynecological cancer. All the patients received platinum and taxane-based chemotherapy: 28 (82%) of patients received chemotherapy as the first line treatment and 6 (18%) of patients received as ≥ two lines of chemotherapy. Eighteen (53%) of patients had one or more comorbidities (hypertension, diabetes mellitus, cardiac disease or pulmonary disease). Hypertension was the most common comorbidity (16 [47%] patients). The ECOG-PS score of all patients was 0, except for one patient, with a score of 1.

Chemotherapy toxicity

At least one grade 3 to 5 chemotherapy toxicity occurred in 24 patients (71%), two or more grade 3 to 5 toxicities occurred in 15 patients (44%), and three or more grade 3 to 5 toxicities occurred in 8 patients (24%) (Table 2). Chemotherapy toxicities of all patients are shown in Table 3. Grade 3 to 5 hematologic toxicity occurred in 24 (71%) patients. The most common grade 3 to 5 hematologic toxicity was neutropenia (20 [59%] patients). Grade 3 to 5 nonhematologic toxicity occurred in only one patient (diarrhea, 3%).

Prediction of toxicity by the CARG tool

Each patient was scored according to the CARG toxicity tool (Table 1). The median overall risk score was 6 (range: 4-15). The patients were divided into three groups based on the risk of grade 3 to 5 toxicities, as described in Methods: low-risk (19 [56%] patients), medium-risk (10 [29%] patients), and high-risk (5 [15%] patients). One or more grade 3 to 5 toxicity was observed in 11 (58%), 8 (80%), and 5 (100%) patients in the low-, medium -, and high-risk groups, respectively. Although there was a trend toward significance, we found no significant difference in the incidence of grade 3 to 5 toxicities among groups (p=0.136) (Figure 1A). However, there was a significant difference in the incidence of two or more grade 3 to 5 toxicities among the risk groups (p=0.0479) (Figure 1B). The difference of the incidence of three or more grade 3 to 5 toxicities among the risk groups was more significant (p=0.0018) (Figure 1C).

Table 3. Chemotherapy toxicities (NCI-CTC 4.0)

Toxicity type	*All grades n (%)*	*Grade 3 to 5 n (%)*
Hematologic		
Anemia	32 (94)	12 (35)
Leucopenia	30 (88)	11 (32)
Neutropenia	30 (88)	20 (59)
Thrombocytopenia	20 (59)	2 (6)
Febrile neutropenia	4 (12)	4 (12)
Nonhematologic		
Nausea	10 (29)	0 (0)
Vomiting	0 (0)	0 (0)
Diarrhea	8 (23)	1 (3)
Neurotoxicity	13 (38)	0 (0)
Elevated creatinine	3 (9)	0 (0)

NCI-CTC 4.0: National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0

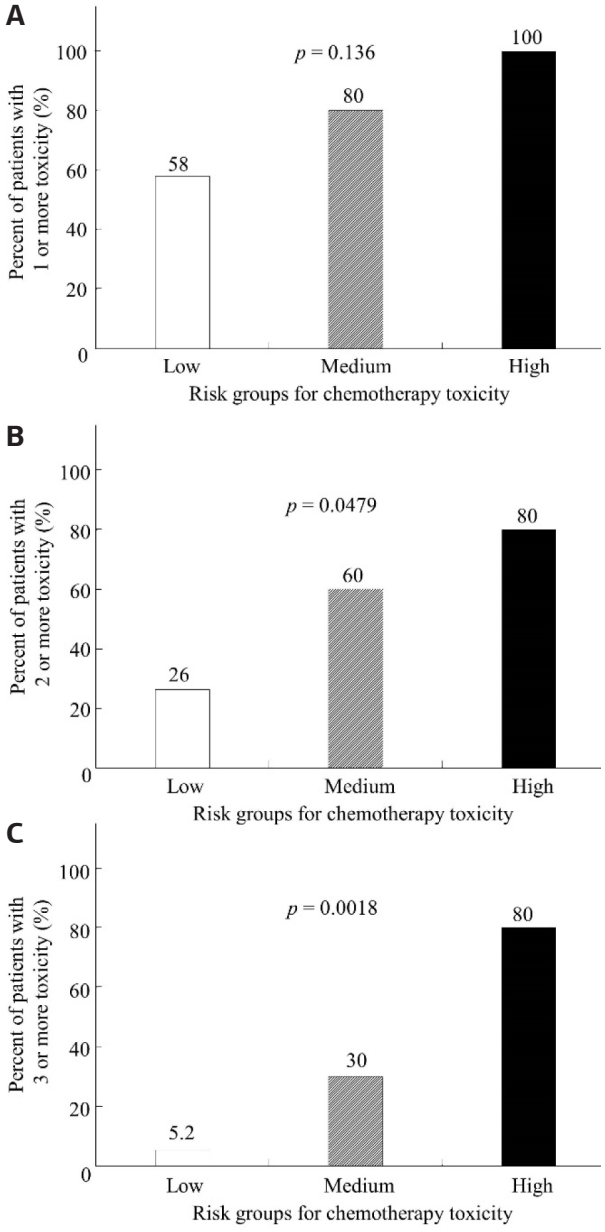

Figure 1. Percentage of patients with severe chemotherapy toxicities among each risk group of the CARG toxicity tool. **A:** Percentage of patients with 1 or more grade 3 to 5 toxicities. **B:** Percentage of patients with 2 or more grade 3 to 5 toxicities. **C:** Percentage of patients with 3 or more grade 3 to 5 toxicities.

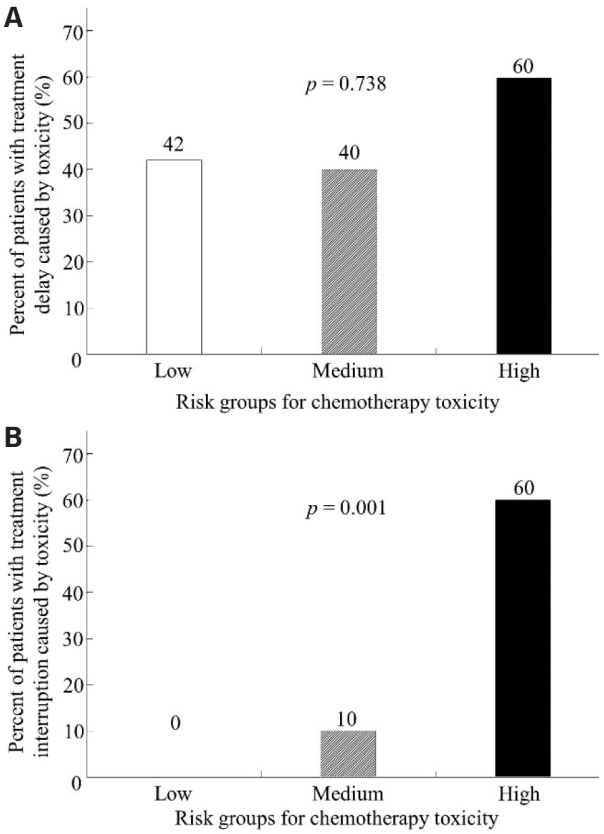

Figure 2. Percentage of patients with treatment delay **(A)** and interruption **(B)** among each risk group of the CARG toxicity tool.

Prediction of treatment delay or interruption by the CARG tool

Although there was no significant difference in the incidence of treatment delay caused by toxicity among the risk groups (p=0.738) (Figure 2A), we found a significant difference in the incidence of treatment interruption caused by toxicity among the risk groups (p=0.001) (Figure 2B).

Discussion

In this study, we made two important clinical findings. We found that the CARG toxicity tool predicted multiple grade 3 to 5 chemotherapy toxicities in older patients with ovarian and endometrial cancer treated with platinum and taxane-based chemotherapy. We also showed that this tool predicted the treatment interruption induced by chemotherapy toxicities.

This study demonstrated that the CARG toxicity tool predicted two or more grade 3 to 5 toxicities caused by chemotherapy in older patients with ovarian and endometrial cancer treated with platinum and taxane-based chemotherapy. Furthermore, this tool predicted more explicitly the incidence of three or more grade 3 to 5 toxicities. The predictive performance of CARG toxicity tool was previously confirmed by development and validation studies [15,17]. However, whether the CARG toxicity tool could predict toxicities for patients with specific tumor types who are receiving specific treatment regimens has been unclear. In this study, we showed that this tool is predictive of the chemotherapy toxicity in older patients with ovarian and endometrial cancer treated with platinum and taxane-based chemotherapy. The usefulness of this score has been also confirmed in older patients with lung cancer [14]. Nie et al evaluated the CARG toxicity tool in the patients receiving chemotherapy for lung cancer. The rates of toxicity were increased across low, intermediate, and high CARG risk groups (9%, 40%, and 60% respectively, p<0.001).

ECOG-PS is conventional oncology performance status measure that is sometimes used for deciding whether to administer the chemotherapeutic agents. However, the ECOG-PS scores of all patients in this study were zero, except for one patient (score=1). Therefore, the ECOG-PS score could not identify older patients at increased risk for chemotherapy toxicity in this study. KPS is another commonly used oncology performance status measure. Several studies have suggested that KPS did not predict the chemotherapy toxicity in older patients [14,15]. Our results and previous studies suggest that conventional oncology performance status measures are not able to predict chemotherapy toxicity, especially in older cancer patients.

Some studies reported a lack of predictive performance of the CARG toxicity tool. Alibhai et al evaluated the tool in a cohort of 46 patients treated with docetaxel for metastatic prostate cancer [20]. The authors did not find a significant increase in toxicity across low, intermediate, and high risk groups (0%, 17%, and 27% respectively, p=0.65). However, only 20% of patients in their study experienced grade 3 to 5 toxicity, which is a very low rate compared with our study and previous reports [15,17]. The low event rate of toxicity may be the reason for their results. Moth et al also reported that CARG toxicity tool did not predict severe chemotherapy toxicities [21]. Their study had a sufficient sample size and event rate; however, their study population included patients with varied cancer types treated with varied chemotherapies, which may be a reason for the different results compared with our study.

CGA is a detailed geriatric assessment to identify clinical predictors of morbidity and mortality [16]. However, this assessment has not been used in everyday oncology practice to predict the chemotherapy toxicity of older cancer patients, because of

the time and resource requirements. In our study, completion of the CARG toxicity tool only required 5 minutes. Therefore, this tool is more suitable for regular daily practice of gynecologic oncologists.

Our study also suggested that the CARG toxicity tool predicted the treatment interruption induced by chemotherapy toxicities. Unexpected treatment interruption caused by chemotherapy toxicities impairs the quality of the cancer therapy. Dose intensity, which is important for the efficacy of chemotherapy [22], is decreased by unexpected interruptions. Therefore, predicting the possibility of treatment interruption would be useful to clarify the treatment decision-making or treatment modifications such as dose reduction.

Although we observed a statistically significant difference in the incidence of multiple grade 3 to 5 toxicities among the risk groups, there was no significant difference in the incidence of at least one grade 3 to 5 toxicity. These results may be due to our small sample size. Generally, the risk of chemotherapy for patients is usually increased in almost direct proportion to the number of severe toxicities. In this study, all patients whose treatment was interrupted by chemotherapy toxicities had multiple adverse events. Thus, predicting the occurrence of multiple severe toxicities is important in everyday practice.

In conclusion, our study confirmed that the CARG toxicity tool was able to predict chemotherapy toxicity in older patients with ovarian and endometrial cancer treated with platinum and taxane-based chemotherapy. Our study suggests that this tool is useful for the gynecologic oncologist in everyday practice. Further studies with large population and other chemotherapy regimens will be required to assess the utility of the CARG toxicity tool in informing oncologist decisions and ensuring safe and effective chemotherapy to older cancer patients.

Conflict of interests

The authors declare no conflict of interests.

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